Pharmacy Update
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In This Issue

Propafenone (Rythmol™): A Brief Review

Introduction

Propafenone is an antiarrhythmic with structural similarities to propranolol, a beta-receptor blocker. It is available in scored, film-coated tablets of 150-mg, 225-mg, and 300-mg strengths manufactured by Knoll Pharmaceuticals.

Indications

Propafenone is indicted for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia. Due to its proarrhythmic effect, use should be reserved for patients in whom the benefits of treatment outweigh the risks. Although not approved for this indication, propafenone has also been used in treating supraventricular tachycardias, including atrial fibrillation and flutter and arrhythmias associated with Wolff-Parkinson-White syndrome.

Pharmacology

Propafenone is a Class IC antiarrhythmic with local anesthetic effects and direct stabilizing action on myocardial membranes. Its electrophysiological effect manifests itself in reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces fast inward current carried by sodium ions. Diastolic excitability threshold is increased, and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

Propafenone has beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials, resting heart rate reductions of about 8% were noted at the higher end of the therapeutic plasma concentration. Propafenone causes a dose- and concentration-related decrease in the rate of single and multiple PVCs and can suppress recurrence of ventricular tachycardia. It also possesses negative inotropic properties and can decrease left ventricular ejection fraction.

Pharmacokinetics

Propafenone is well absorbed from the gastrointestinal tract, producing peak serum levels in 2 to 3 hours. Serum levels have not correlated well with clinical response. The drug is metabolized in the liver with only small amounts (1%) appearing unchanged in the urine. The metabolism of propafenone is genetically determined. The elimination half-life is 5 to 8 hours in extensive metabolizers, and approximately 17 hours in poor metabolizers.

Selected Clinical Studies

A recent study published in the *American Journal of Cardiology* supports the unlabeled use of propafenone for treatment of new-onset atrial fibrillation (AF). This trial compared oral loading doses of propafenone and amiodarone for converting recent-onset atrial fibrillation. This was a prospective, randomized, multicenter study comparing the time to conversion to sinus rhythm obtained with an oral loading dose of propafenone or amiodarone. Patients with recent-onset AF (<2 weeks) were randomly assigned to be treated with propafenone (600 mg for the first 24 hours and if necessary a repeated dose of 300 mg for 24 hours) or amiodarone (30 mg/kg for the first 24 hours and if necessary a repeated dose of 15 mg/kg for 24 hours). The median time for restoration of sinus rhythm was shorter ($p=0.05$) in the propafenone (2.4 hours) than in the amiodarone (6.9 hours) group. After 48 hours the same proportion of patients in the two groups recovered sinus rhythm.

The UK Propafenone PSVT Study Group conducted a randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia (PSVT) and paroxysmal atrial fibrillation (PAF). Patients were randomized into two consecutive crossover periods of propafenone (300 mg BID) versus placebo followed by 300 mg TID propafenone versus placebo. Analysis was based on the time to treatment failure, defined as the interval from treatment onset to the occurrence of either ECG-documented arrhythmia or an intolerable adverse event. Propafenone reduced the rate of both PAF and PSVT as described in Table 1. There was a greater incidence of adverse events noted in the high dose propafenone group. The lower dose of 300 mg BID was effective and well tolerated.

Table 1. UK Propafenone PSVT Study Group

	Propafenone	Placebo
PAF	**n=30**	**n=30**
Percent attack free	53%	13%
Median time to first recurrence	>98days	8 days
PSVT	**n=45**	**n=45**
Percent attack free	47%	16%
Median time to first recurrence	>98days	12 days

Adverse Effects

Adverse reactions associated with propafenone occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. Approximately 20% of patients discontinue therapy because of adverse reactions. The most common events were unusual taste, dizziness, intraventricular conduction delay, nausea and/or vomiting, and constipation. Headache was relatively common but was not increased compared to placebo. Less common reactions included first-degree AV block, congestive heart failure, dyspepsia, and weakness.

Drug Interactions

Quinidine – Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients slow propafenone metabolizers. There is too little information to recommend concomitant use of propafenone and quinidine.

Local Anesthetics – Concomitant use of local anesthetics may increase the risks of central nervous system side effects.

Digitalis – Propafenone produces dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone. Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin dosage should ordinarily be reduced when propafenone is started.

Beta-Antagonists – Concomitant administration of propafenone and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels. While the therapeutic range for beta blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

Warfarin – In patients receiving propafenone and warfarin concomitantly, mean steady state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of 25%. Prothrombin times should be monitored routinely, and the dose of warfarin adjusted accordingly.

Cimetidine – Concomitant administration of propafenone and cimetidine resulted in a 20% increase in steady-state plasma concentrations of propafenone with no change in electrocardiographic parameters.

Desipramine – Both desipramine and propafenone are cleared by oxidative pathways of demethylation and hydroxylation carried out by hepatic P-450 cytochromes. Administration of both agents together may result in elevated serum desipramine levels.

Cyclosporine – Propafenone therapy may increase cyclosporine serum concentrations.

Theophylline – Propafenone may increase theophylline concentrations during concomitant therapy.

Rifampin – Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

Other – Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Precautions and Contraindications

Propafenone is contraindicated in patients with uncontrolled CHF; cardiogenic shock; sinoatrial, AV, and intraventricular disorders of impulse generation or conduction (e.g., sick sinus node syndrome, AV block) in the absence of an artificial pacemaker; bradycardia; marked hypotension; bronchospastic disorders; electrolyte imbalance; and hypersensitivity to the drug.

Dosage and Administration

For sustained ventricular arrhythmia, a propafenone dose of 150 mg every 8 hours is given. Dosage may be increased at a minimum of 3-4 day intervals to 225 mg every 8 hours and, if necessary, to 300 mg every 8 hours. The dose should be gradually titrated according to response and tolerability.

For recent-onset atrial fibrillation, a single dose of 600 mg is used for the first 24 hours. If necessary, a 300-mg dose is given after 24 hours.

Table 2. Propafenone NIH Acquisition Cost

Strength	Cost Per 100 Tablets
150 mg	$54.37
225 mg	$77.62
300 mg	$99.04

Conclusion

Propafenone is an effective antiarrhythmic drug capable of restoring normal sinus rhythm in patients with PAF or PSVT. Due to the potential for proarrhythmic effects, this agent should be used with caution.

References available upon request.

Preventing Chemotherapy-related Medication Errors

What is our philosophy about preventing chemotherapy-related medication errors?

- Take a proactive approach and examine our chemotherapy ordering, preparation, and administration systems on a regular basis even though we do not have a known problem with chemotherapy-related medication errors.
- Use prescribing error, near-miss, and hospital occurrence data in a proactive manner to improve the system.

How do we prevent chemotherapy-related medication errors?

Multidisciplinary, independent checking at each step of the process:

Prescribing

- Educate prescribers about error prevention
- Standardize nomenclature for dosage expression in protocol and order
- Create protocol-specific, physician order entry screens
- Automate dose calculations
- Pharmacist checks order against protocol independently from prescriber

Preparation and Dispensing

- Educate pharmacists and technicians about error prevention
- Check preparation workcard (two pharmacists assisted by a checklist)
- Re-check calculations at preparation (technician)
- Check product against order (pharmacist assisted by a checklist)
- Educate patient when dispensing oral chemotherapy medications

Administration

- Educate nurses about error prevention
- Computer-generated care plan
- Check order against protocol (nurse); second nurse verifies order
- Check product label against order (nurse); second nurse verifies label
- Verify infusion pump settings, if applicable (two nurses)
- Nurse checks chemotherapy during infusion (e.g., blood return, assess IV site)
- Educate patient about chemotherapy regimen verbally and through informed consent

How we monitor our performance?

- *Quantify* prescribing errors and *Classify* by potential error severity
- Serious (Class I) errors are reported with full details
- Quarterly summaries and analysis provided for Class II and III errors
- Analyze "near-miss" situations
- Analyze hospital occurrence reporting system data

How we use the information?

An interdisciplinary committee, under the direction of the medical staff, recommends and implements changes to the system based on error patterns identified.

How have we done so far?

Since 1996, we have implemented over 20 changes (e.g., created dose-calculation screens) to the chemotherapy ordering, preparation, and administration systems and have documented an overall 10% decrease in prescribing errors and 50% decrease in serious (Class I) prescribing errors. The most significant decrease in serious prescribing errors has been demonstrated for protocols with dose-calculation ordering screens.

Where are we going next?

An expanded, interdisciplinary committee covering NCI's Medicine, Pediatric, and Surgery Branches and NHLBI's Bone Marrow Transplant Unit, met in June to review our current system. Additional system changes (e.g., develop a hospital-wide "chemotherapy" policy) were recommended. These recommendations were endorsed by the Pharmacy & Therapeutics Committee and will be implemented over the coming year.

Medication Utilization Evaluation: Omeprazole (Prilosec®)

Omeprazole (Prilosec®) is a substituted benzimidazole compound with potent anti-secretory properties. It suppresses gastric acid secretion by inhibiting the H+/K+ ATPase enzyme system (proton pump) at the surface of the gastric parietal cell. Omeprazole has been available at the Clinical Center since 1989. Use of omeprazole has increased as the number of approved indications for the drug has increased. The Pharmacy & Therapeutics Committee undertook a review of omeprazole use at the Clinical Center in 1996 and concluded that omeprazole prescribing, where clearly documented in the medical record, was appropriate. Omeprazole accounted for $406,480 of the Pharmacy Department's drug budget for fiscal year 1999, an 145% increase from 1995. The Pharmacy and Therapeutics Committee recently undertook another review of omeprazole use.

The Committee, in cooperation with the NIDDK Digestive Disease Branch, approved guidelines for the use of omeprazole. The following indications were considered appropriate justifications for the use of omeprazole:

- Endoscopically proven gastric ulcer refractory to treatment for 8 weeks with histamine H_2-receptor antagonist
- Endoscopically proven duodenal ulcer refractory to treatment for 8 weeks with histamine H_2-receptor antagonist or sucralfate
- Endoscopically proven grade 3 or 4 reflux esophagitis
- Endoscopically proven reflux esophagitis refractory to treatment for three months with histamine H2-receptor antagonist
- Hypersecretory conditions (e.g., multiple endocrine adenomas, systemic mastocytosis, Zollinger-Ellison Syndrome)
- Endoscopically proven Barrett's esophagus
- *Helicobacter pylori* eradication in conjunction with antimicrobial agents

In addition, the following indications were considered appropriate justification for prescribing omeprazole at the Clinical Center:

- Continuation of therapy
- Protocol use
- ICU stress prophylaxis

Methods

A prospective review of orders for omeprazole was conducted. New orders for inpatients

for whom omeprazole was prescribed between January and March were reviewed. Basic demographic data regarding patients and prescribers were collected. Additionally, information about the indication for omeprazole use and the dose regimen were collected.

Results

Of the 53 orders reviewed, 45 contained sufficient documentation about omeprazole to be considered evaluable. In 34 of these cases, omeprazole was prescribed appropriately for indications consistent with the Clinical Center guidelines. The dosage regimen in each of these cases was also considered appropriate.

Conclusions

Omeprazole prescribing at the Clinical Center is not always appropriate. The indications for omeprazole use are sometimes not clearly documented in the medical record. Considering the increased use of omeprazole and its relatively high cost, this drug should be used in accordance with the established guidelines. Furthermore, the indication for omeprazole use (and for all medications) should be documented clearly in the medical record.

Drug Information Service

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FDA Safety Reports

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- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov*. In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Pramipexole (Mirapex), an oral nonergot dopamine receptor agonist for advanced Parkinsonism
- Oseltamivir (Tamiflu), an oral neuraminidase inhibitor for treatment of influenza
- Ibutelide (Covert), an injectable predominantly class III antiarrhythmic
- Propafenone (Rythmol), an oral class IC antiarrhythmic
- Isosorbide Mononitrate (Imdur, others), an oral vasodilator for chronic, stable angina
- Dapiprazole (Rev-Eyes), an ophthalmic alpha-adrenergic blocker for treatment of iatrogenically induced mydriasis
- Montelukast (Singulair), an oral leukotriene-receptor antagonist for treatment of asthma
- Glyburide/Metformin (Glucovance), an oral combination product for treatment of type 2 diabetes

Editors' Note

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